IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2005_0152A
Sadanobu SHIRAI et al.	:	**Confirmation No. 3564**
Serial No. 10/524,858	:	Group Art Unit 1615
Filed February 18, 2005	:	Examiner Hasan Syed Ahmed
PATCHES CONTAINING TULOBUTEROL	:	**Mail Stop: AMENDMENT**

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Office Action of June 16, 2010, the time for responding thereto being extended for one month in accordance with a Petition for Extension of Time submitted herewith, Applicants submit the following remarks in support of the patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims. Further and favorable reconsideration is respectfully requested in view of these remarks.

The Present Invention

The present invention relates to a patch containing tulobuterol prepared by laminating an adhesive layer consisting of a rubber, a non-acrylic adhesive resin such as petroleum resin, polyterpene resin, polyolein resin and saturated alicyclic hydrocarbon resin, and a plasticizer on a backing, wherein 1 to 4 w/w% of tulobuterol as an active ingredient and 0.1 to 3 w/w% of a higher fatty acid such as a C_{11-22} fatty acid as a drug release controlling agent are contained in the adhesive layer.

The patch of the present invention is characterized by containing tulobuterol in such a low concentration as 1 to 4 w/w% as well as a higher fatty acid such as a C_{11-22} fatty acid as a drug release controlling agent, and by showing sufficient, stable and controlled release of tulobuterol despite the fact that tulobuterol is contained in a low concentration.

Claim rejection under 35 USC § 103

The rejection of claims 1-4 under 35 U.S.C. § 103(a) as being unpatentable over Hoffmann et al. (hereinafter "Hoffmann") in view of Higo et al. (hereinafter "Higo"), and further in view of Stroppolo et al. (hereinafter "Stroppolo") is respectfully traversed.

(1) Comparison with US Patent 5,254,348 (Hoffmann)

This patent relates to a preparation for asthma therapy containing tulobuterol as an active ingredient, more in detail, a transdermal therapeutic system with tulobuterol or one of the pharmaceutically acceptable salts thereof as an active substance, comprising a backing layer which is substantially impermeable to the active substance and at least one matrix layer which comprises at least one styrene-1,3-diene-styrene block copolymer.

The object of Hoffmann's invention is to provide a transdermal therapeutic system with tulobuterol suitable for asthma therapy, which is achieved by a transdermal therapeutic system comprising as an active substance tulobuterol in a matrix containing at least one polystyrene-1,3-diene-polystyrene block copolymer (column 2, lines 46 to 53).

The only point of Hoffmann's invention is to use polystyrene-1,3-dienepolystyrene block copolymer in a matrix comprising as an active substance tulobuterol in a transdermal therapeutic system suitable for asthma therapy, and nothing else.

As **solubilizers and plasticizers,** various kinds of substances such as fatty acids, mineral oil, glycerol, paraffins and so on are merely illustrated (enumerated) in this patent (column 3, lines 58 to 65). However, the description of fatty acids is not found in any other part of the description other than column 3, lines 58 to 65.

It cannot even be speculated from this patent that higher fatty acids, especially C_{11-22} fatty acids are used as a release controlling agent for tulobuterol. Especially, even the plasticizer or the solubilizer is not used in any example in this patent.

It is therefore clear that the solubilizers and plasticizers are neither essential nor important for the invention of Hoffmann, and there is no rational reason that the fatty acids are especially selected from the disclosure of Hoffmann in order to combine them with the disclosure of Higo mentioned below.

(2) US Patent 5,866,157 (Higo)

Higo discloses a matrix type patch formulation which comprises an adhesive layer containing a physiological active substance (0.1-20%w/w), an organic acid including its water-soluble salt (0.01-15%), a hydrophobic high molecular material (15-60%), a tackifying resin (10-70%), a plasticizer (10-60%) and an absorption enhancer (0.01-20%) (column 2, lines 40 to 52).

The object of Higo's invention is to provide a matrix type patch formulation which increases percutaneous absorbability of the physiological active substance and is extremely reduced in irritation to skin where the formulation is applied (column 2, lines 24 to 29). The patent describes that the inventors "... found that the percutaneous permeable property of drug is significantly improved…by formulating a physiological active substance, **an organic acid and an absorption enhancer** into an adhesive layer…" (column 2, lines 32 to 39) (emphasis added).

As explained above, Higo's invention is characterized by increasing percuteneous permeability of a physiological active substance such as tulobuterol by formulating **an organic acid and an absorption enhancer** into the adhesive layer. This object of Higo's invention (increase of permeability of the active substance) can be attained by using **a combination of an organic acid and an absorption enhancer.**

As shown in Table 1 with regard to Comparative Examples 1-13 in Higo, the objective and desired effect of the invention is not attained by using **either an organic acid** such as sodium propionate (C. Ex. 7, 11 and 13), sodium acetate (C. Ex. 8, 10 and 12) and sodium salicylate (C. Ex. 9) **or an absorption enhancer** such as pirotiodecane (C. Ex. 1,2 and 3), 1-menthol (C. Ex. 4 and 5) and lauryl alcohol (C. Ex. 6). Namely, to use either (only) one is clearly excluded from Hugo's invention, and therefore, the inventive idea to use either one does not arise from this patent. This object of Higo's invention can be attained by using **a combination of an organic acid and an absorption enhancer.**

In addition, although the organic acid does not exclude a higher fatty acid as it is mentioned that as "examples of the organic acid…aliphatic (mono, di, tri) carboxylic acids…may be exemplified" (paragraph bridging columns 2-3), it is usually difficult to choose a higher fatty acid from the term "an organic acid and an absorption enhancer".

As indicated by the Examiner, a higher fatty acid such as C_{11-20} fatty acid is illustrated as one of many many various **absorption enhancers** of a physiological active substance therein. However, as the most preferable ones, **1-menthol, lauryl alcohol and pirotiodecane** are

illustrated (column 5, lines 21 to 22). Further, these compounds are used with an organic acid in the working examples. However, the higher fatty acid is never used as an absorption enhancer in any working example therein. Furthermore, as explained above, when these absorption enhancers are solely admixed in the composition [pirotiodecane (C. Ex. 1, 2 and 3), 1-menthol (C. Ex. 4 and 5) and lauryl alcohol (C. Ex. 6)], the transdermal permeation rate of the drug decreases **drastically** as shown in Table 1 of this patent.

Furthermore, according to the disclosure of the present specification, with respect to the Comparative example 6 containing **isopropyl myristate** (page 14), which is illustrated in Higo as one of the absorption enhancers, it shows a 44% permeation rate of the drug as shown in Table 1 (page 17). Comparative example 6 is much influenced by changes of preservation temperature as compared with the present invention (Example 1: 89% in rate of the drug permeated).

One skilled in the art would not be led to select only the higher fatty acid from among many various absorption enhancers including isopropyl myristate despite the fact that the fatty acids are used for different purposes between Hoffmann and Higo; and to solely use an absorption enhancer would be avoided and the effect achieved by the present invention would not be expected. There is no rational reason that the fatty acids are especially selected from the disclosure of Higo in order to combine them with the disclosure of Hoffmann. Applicants respectfully submit that the Examiner's conclusion is based on improper hindsight reasoning.

In addition, in this patent, there is the description that as a tackifying resin, glycerin esters of rosin are most preferable (column 4, lines 25 to 27). As the hydrophobic high molecular material, acrylic polymer may be exemplified (column 3, line 4 from the bottom to column 4 line 8). Accordingly, the Examiner's statement that "Higo does not require acrylic adhesives" in the Office Action at page 4, line 6 should be withdrawn.

According to the present invention, as mentioned at page 5, lines 4 to 13:

> "In regard to patches containing tulobuterol which have been traditionally proposed, it has been considered that it is essential to blend an acrylic adhesive which has a large polar or reactive group, or an adhesive resin having a large polarity such as a rosin in an adhesive layer.
>
> However the patch related to the present invention does not need such substances, and that it is found that to blend such substances in an adhesive layer is

not rather preferable because such substances cause to give great influences to release pattern of tulobuterol and stability in changes of the passage with time."

It is therefore impossible for the skilled person in the art to have expected that, instead of a combination of **an organic acid and an absorption enhancer** described in Higo, by using a higher fatty acid such as a C_{11-22} fatty acid alone, a patch containing tulobuterol in a low concentration and having stable release controllability would be prepared. From the disclosure of Higo, one would not be motivated to use such a C_{11-22} fatty acid alone with the expectation of obtaining the improved patch preparation containing tulobuterol of the present invention (claims 1 to 3).

(3) Comparison with US Patent 5,312,627 (Stroppolo)

According to the Office Action, the Examiner states that:

"Stroppolo… teaches plasticizers (e.g. polyethylene glycols) at a concentration of 4-20%...Stroppolo teaches a transdermal therapeutic system for releasing, *inter alia,* turobuterol. Stroppolo does not require acrylic adhesives and does not disclose them in any of the examples".

However, even taking the Examiner's statement at face value, the patentability of the presently claimed invention has not been established in view of the distinctions between the present invention and the Hoffmann/Higo references as discussed above.

(4) Unexpected result

As shown in Fig. 1 (according to test 1) of the present invention, the patch of the present invention (Example 1) maintains a tulobuterol level in serum as much as a commercialized tulobuterol-patch in concentration of one-fifth the tulobuterol concentration of the commercialized patch.

With respect to Comparative example 6 in the present specification, containing isopropyl myristate, which is illustrated in Higo as one of the absorption enhancers, it shows a 44% permeation rate of the drug as shown in Table 1 (according to test 3) of the specification. Comparative example 6 is much influenced by changes of preservation temperature as compared to the present invention (Example 1:89% in permeation rate of the drug).

With respect to Comparative example 4 containing no higher fatty acid, it shows a 162% permeation rate of the drug as shown in Table 1 (according to test 3) of the present invention. Comparative example 4 is very influenced by changes of preservation temperature as compared to the present invention (Example 1:89% in permeation rate of the drug).

Thus, it is clearly shown in the present specification that the present invention (claims 1 to 3) achieve an unexpected effect.

(5) Combination of Hoffmann in view of Higo, further in view of Stroppolo

The Examiner concluded that it would have been obvious to a person of ordinary skill in the art to modify the teachings of Hoffmann with the teachings of Higo to arrive at C_{11-22} fatty acids at a concentration of 0.01-20% since both references teach transdermal formulations comprising, *inter alia,* a low concentration of tulobuterol and fatty acids.

Further, the Examiner concluded that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare a patch consisting of rubber, an adhesive resin other than an acrylic adhesive, a plasticizer, tulobuterol, and a higher fatty acid, as taught by Hoffmann in view of Higo, further in view of Stroppolo.

However, as explained above, the subject matter of the present invention is completely different from Hoffmann's invention in the point of using a higher fatty acid as a release controlling agent for tulobuterol. Further the subject matter of the present invention is patentably different from Higo in the point of excluding ("consisting of" in claim 1) a combination of an organic acid and an absorption enhancer.

Therefore, the skilled person in the art would not be motivated to combine Hoffmann, Higo and Stroppolo, and even if these references are combined, it would not be possible for a skilled person to combine 1 to 4 w/w% of tulobuterol, a rubber, a non-acrylic adhesive resin, a higher fatty acid, and a plasticizer into a patch formulation expecting the excellent effect such as controllability of stable drug-release of the present invention.

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the Application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Sadanobu SHIRAI et al.

/Andrew B. Freistein/

Digitally signed by /Andrew B. Freistein/
DN: cn=/Andrew B. Freistein/, o=WLP, ou=WLP, email=afreistein@wenderoth.com, c=US
Date: 2010.10.18 14:42:21 -04'00'

By _____

Andrew B. Freistein
Registration No. 52,917
for
Michael R. Davis
Registration No. 25,134
Attorney for Applicants

ABF/vah
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
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